

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 33

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte TED M. DAWSON, JOSEPH P. STEINER
VALINA L. DAWSON, GEORGE R. UHL
and SOLOMON H. SNYDER

Appeal No. 1997-3122
Application No. 08/082,848¹

HEARD: November 16, 2000

Before WINTERS,² ROBINSON and SCHEINER, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

¹ Application for patent filed June 30, 1993.

² Appellants' oral argument was heard by Administrative Patent Judges Robinson, Spiegel and Scheiner on November 16, 2000. Subsequently, appellants submitted paper no. 32, indicating that "the Public Health Service as represented by the Office of Technology Transfer, having an address at National Institutes of Health . . . is the co-owner of an undivided interest in the subject application, along with the Johns Hopkins University." As the result of this information, Judge Spiegel has recused herself from the case, and Judge Winters will substitute for her on the panel deciding this appeal.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 through 9 and 17 through 25. Claims 11 through 16, while still pending, have been withdrawn from consideration as directed to non-elected subject matter. Claims 1, 7 through 9 and 17 are representative of the subject matter on appeal and are reproduced below:

1. A method for inhibiting glutamate-mediated neurotoxicity mediated by N-methyl-D-aspartate (NMDA) receptors in vascular stroke and neurodegenerative disease patients, comprising:
administering to a vascular stroke or neurodegenerative disease patient a drug which upon binding to an immunophilin inhibits calcineurin, in an amount effective to inhibit glutamate-mediated neurotoxicity mediated by NMDA receptors.

7. The method of claim 1 wherein the patient is a vascular stroke patient.

8. The method of claim 1 wherein the patient is a neurodegenerative disease patient.

9. The method of claim 8 wherein the neurodegenerative disease is selected from the group consisting of Huntington's Disease, Alzheimer's Disease, and Parkinson's Disease.

17. A method for inhibiting glutamate-mediated neurotoxicity mediated by N-methyl-D-aspartate (NMDA) receptors in vascular stroke and neurodegenerative disease patients, comprising:
administering to a vascular stroke or neurodegenerative disease patient a drug which upon binding to an immunophilin inhibits calcineurin, in an amount effective to inhibit calcineurin.

Claims 1 through 9 and 17 through 25 stand rejected under 35 U.S.C. § 112, first paragraph as based on a non-enabling disclosure.

We reverse the examiner's rejection.

BACKGROUND

“Glutamate, the major excitatory neurotransmitter in the brain, acts through several receptor subtypes.” “[A]cting at [the] N-methyl-D-aspartate (NMDA) subtype of receptors, [glutamate] is responsible for neurotoxic damage in vascular strokes,” as demonstrated by the fact that “selective antagonists of NMDA glutamate receptors prevent neuronal cell death in animal models of hypoxic-ischemic brain injury.” “Glutamate mediated neurotoxicity has also been implicated in neurodegenerative disorders such as Alzheimer’s and Huntington’s diseases.” Specification, pages 1 and 2 (citations omitted).

It is also recognized that “[d]uring the normal course of a vascular stroke or neurodegenerative disease, glutamate released from adjacent nerve terminals activates the NMDA subclass of glutamate receptors to increase intracellular Ca^{+2} . . . [t]he Ca^{+2} binds to calmodulin, activating NOS [nitric oxide synthase] . . . Ca^{+2} entry also activates calcineurin, which dephosphorylates and activates NOS.” “The NO [nitric oxide] generated by NOS diffuses to adjacent cells,” which die “[i]f sufficient quantities of NO are produced.” Specification, page 4. Finally, it has been shown that “inhibitors of nitric oxide synthase prevent neuronal cell death.” Specification, page 2.

Immunophilins, e.g., cyclophilin and FK-506 binding protein (FKBP), are “[h]igh-affinity receptor proteins in the cytoplasm that combine with such immunosuppressants as cyclosporin A, FK506, and rapamycin . . . [they] are important in transducing signals from the cell surface to the nucleus . . . [and] [d]rug-immunophilin complexes are implicated in

the mechanism of action of the immunosuppressant drugs, cyclosporin, FK506, and rapamycin.”³ “Besides their role in the immune system, . . . cyclophilin and [FKBP] are highly concentrated in the brain in discrete neuronal structures where they are co-localized with the Ca^{+2} activated phosphatase, calcineurin,” and it has been demonstrated that “FK-506 and cyclosporin A, which bind to FKBP and cyclophilin, respectively, inhibit calcineurin, and . . . both drugs enhance the phosphorylation of a number of proteins in the brain.” Specification, page 2 (citations omitted).

According to page 4 of the specification,

It is a discovery of the present invention that immunosuppressant-type drugs, such as FK-506 and cyclosporin A, which bind to immunophilins, block glutamate neurotoxicity that is mediated by N-methyl-D-aspartate (NMDA) receptors. Upon binding of FK-506 and cyclosporin A to their respective immunophilins (binding proteins), the activity of the calcium-activated phosphatase calcineurin is inhibited. Thus treatment with this class of drugs increases the phosphorylation of proteins which are substrates of calcineurin. It is a further discovery of this invention that phosphorylated nitric oxide synthase (NOS) is a substrate for calcineurin. A model which accounts for these findings is that immunosuppressant-type drugs block neurotoxicity by inhibiting calcineurin, thereby increasing the phosphorylation of NOS, thereby inhibiting production of nitric oxide.

The specification contains various examples demonstrating that NOS is a substrate for calcineurin and that FK-506 enhances phosphorylation of NOS (Example 1); that FK-506 and cyclosporin A, but not rapamycin, markedly diminish NMDA neurotoxicity in primary cerebral cortical neuronal cultures (Example 2); and that enhanced

³ Illustrated Dictionary of Immunology, J.M. Cruse and R.E. Lewis (eds.), CRC Press, Boca Raton, Florida, 1995, “immunophilins,” page 163 (copy attached).

phosphorylation of NOS by FK-506 diminishes functional NO activity in neuronal cultures (Example 3).

Based on these examples, appellants conclude that “immunophilin-binding drugs, by inhibiting calcineurin, cause the enhanced phosphorylation of NOS, thereby leading to lowered nitric oxide production” and that “immunophilin-binding, calcineurin-inhibiting drugs may be used therapeutically to treat neurotoxicity mediated through NMDA-type glutamate receptors.” Specification, page 13.

Enablement

In its broadest aspect, the present invention is directed to inhibiting glutamate- and NMDA receptor-mediated neurotoxicity in vascular stroke and neurodegenerative disease patients by administering a drug which binds to an immunophilin and inhibits calcineurin, in an amount effective to inhibit glutamate-mediated neurotoxicity or to inhibit calcineurin (e.g., claims 1 and 17).⁴ According to the examiner, however, “the disclosure is enabling only for claims limited to methods for blocking glutamate-mediated neurotoxicity mediated by N-methyl-D-aspartate (NMDA) receptors in cortical neurons by administering FK506.” Examiner’s Answer, page 5.

If we can summarize the examiner’s position, it is that the amount of direction or guidance supplied by the specification, including the working examples discussed above,

⁴ According to the specification, neurodegenerative diseases include Huntington’s disease, Alzheimer’s disease and Parkinson’s disease (page 5).

is quite limited given the breadth of the claims, and on the whole, insufficient to enable the breadth of claimed invention without undue experimentation; in particular, the specification is insufficient to establish “that the in vitro system used is predictive of in vivo administration . . . [or] representative . . . of neurotoxicity in Huntington’s disease, Alzheimer’s disease, or Parkinson’s disease.” Examiner’s Answer, pages 6 and 7.

“The first paragraph of 35 U.S.C. § 112 requires, inter alia, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without ‘undue experimentation.’ In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is ‘undue.’” In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original).⁵ Nevertheless, “[w]hen rejecting a claim

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Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatApplnt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(continued...)

under the enablement requirement of section 112,” it is well settled that “the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.” In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Thus, the dispositive issue here is not whether appellants have established that their disclosure is broadly enabling for the scope of the claims, or whether it is predictive or representative of in vivo results, rather, the issue is whether the PTO has met the “initial burden of setting forth a reasonable explanation as to why” it is not. Keeping this in mind, we consider the specific reasons provided by the examiner in support of her position.

First, the examiner acknowledges that the claims require administration of a drug “which upon binding to an immunophilin inhibits calcineurin,” but finds that “the specification does not provide guidance in selecting those drugs other than FK-506 that would meet the functional limitations of the claims,” thus, it would “constitute undue experimentation to identify all drugs which bind to an immunophilin where the binding results in inhibiting calcineurin.” Examiner’s Answer, page 8. However, the specification

⁵(...continued)

does provide additional guidance: the specification teaches that the complex formed between cyclosporin A and cyclophilin inhibits calcineurin (on the other hand, the specification teaches that rapamycin is not an appropriate drug for the claimed method, as it binds FKBP, but does not inhibit calcineurin) (pages 8 and 9).

Further, the specification identifies several other immunophilin-binding drugs (page 6) and teaches (with reference to several specific assay protocols) that “[t]he effectiveness of a compound, and its relative potency as a calcineurin inhibitor, can be tested and routinely determined by measuring inhibition of calcineurin activity, for example, by monitoring the level of phosphorylation of NOS in cerebellar homogenates or cultured neuronal cells . . . [a]lternatively, compounds can be tested to determine whether they inhibit the amount of NO formed, cGMP formed, or cell death occurring after treatment with glutamate or NMDA” (page 5).

We accept, for the sake of argument, that it would be time consuming to determine which of the many known immunophilin-binding drugs also inhibit calcineurin. Nevertheless, the examiner does not question the ability of one skilled in the art to follow the disclosed processes. As explained in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), undue experimentation has little to do with the quantity of experimentation; it is much more a function of the amount of guidance or direction provided:

[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation “must not be unduly extensive.” Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982).

In our view, the evidence of record supports appellants’ conclusion that “[t]he experimentation required to determine drugs other than FK-506 and cyclosporin with which to practice the [claimed] method . . . is routine and is not undue” and “the specification provides a reasonable amount of guidance as to how this experimentation should proceed.” Brief, pages 6 and 7.

The examiner additionally relies on Sharkey,⁶ a reference published after the filing date of the present application, to establish “doubt as to the objective truth of appellant[s]’ assertion of predictability.” Examiner’s Answer, page 9. Nevertheless, on balance, we find that Sharkey’s teachings weaken, rather than reinforce, the examiner’s position.

⁶ Sharkey & Butcher (Sharkey), “Immunophilins Mediate the Neuroprotective Effects of FK506 in Focal Cerebral Ischaemia,” Nature, Vol. 371, pp. 336-339 (September 22, 1994).

Sharkey demonstrates that “FK506 is a powerful neuroprotective agent in an in vivo model of focal cerebral ischaemia of equivalent efficacy to the non-competitive NMDA receptor antagonist, MK801,” a known neuroprotective agent.⁷ Page 337, left-hand column. The examiner acknowledges that “[c]ortical damage was inhibited,” but argues that “striatal damage was unaltered by any dose of FK-506 . . . [i]n addition, the ligands cyclosporin and rapamycin failed to protect.” Thus, according to the examiner, “primary cerebral cortical neuronal cultures . . . are not predictive of the in vivo situation for at least stroke in parts of the brain other than the cortex,” nor is the specification enabling for drugs other than FK-506. Moreover, the examiner argues that Sharkey’s results “provide reason to doubt that the claimed method would be suitable for treating [Parkinson’s disease and Alzheimer’s disease] and that the in vitro model of the specification would not be predictive,” because striatal tissue is affected in both diseases.⁸ Examiner’s Answer, page 9.

⁷ According to Sharkey, “[a]nimal models of focal cerebral ischaemia based on middle cerebral artery (MCA) occlusion reproduce the pattern of ischaemic brain damage observed in many human stroke patients” and “[d]amage extends throughout the vascular territory of the MCA: that is, within the striatum and cortex.”

⁸ As evidence of striatal involvement in Parkinson’s disease and Alzheimer’s disease, the examiner cites Ulas et al., “Selective Increase of NMDA-Sensitive Glutamate Binding in the Striatum of Parkinson’s Disease, Alzheimer’s Disease, and Mixed Parkinson’s Disease/Alzheimer’s Disease Patients: An Autoradiographic Study,” The Journal of Neuroscience, Vol. 14, No. 11, pp. 6317-6324 (November 1994).

Appellants, on the other hand, cite Nagasawa⁹ as evidence in support of their argument that “[t]he pattern of blood vessel occlusion in [] stroke models causes any treatment to be less effective in the striatum than in the cerebral cortex.” Brief, page 8. Indeed, Sharkey addresses this very effect: “The finding that brain damage is reduced in cortex but not striatum has been attributed to differences in vascular supply to these brain areas, and is also typical of the actions of neuroprotective drugs tested in MCA occlusion models” (page 337, citations omitted). Inasmuch as blood vessel occlusion “is not the cause of either Parkinson’s disease or Huntington’s disease,”¹⁰ appellants argue that “[a] drug’s lack of effectiveness in the striatum in a stroke model provides no reason to infer that the same drug will not be able to access the striatum in patients who have other neurological diseases.” Brief, page 8. We would add that we see no reason to infer that a drug effective in the cortex will not be effective in the striatum; as acknowledged by the examiner, “the type of damage being treated in the claims (glutamate-mediated neurotoxicity mediated by NMDA receptors) is the same no matter how caused.” Examiner’s Answer, page 10.

⁹ Nagasawa & Kogure (Nagasawa), “Correlation Between Cerebral Blood Flow and Histologic Changes in a New Rat Model of Middle Cerebral Artery Occlusion,” Stroke, Vol. 20, No. 8, pp. 1037-1043, August 1989.

¹⁰ See Beal et al., “Degenerative Diseases of the Nervous System,” in Harrison’s Principles of Internal Medicine, p. 2060, 12th ed., 1991.

With respect to the ineffectiveness of rapamycin in Sharkey's model, we note that Sharkey reasons that "[calcineurin involvement would explain the lack of rapamycin efficacy because a complex of FK506-FKBP12, but not rapamycin-FKBP12, inhibits calcineurin" (page 338). This is consistent with the present specification, which implicates calcineurin in appellants' proposed mechanism of neurotoxicity, and indicates that rapamycin would not be effective in the present method because it does not inhibit calcineurin (Example 2). Finally, with respect to the ineffectiveness of cyclosporin (which does inhibit calcineurin) in Sharkey's model, Sharkey suggests that "the lack of efficacy in this study may reflect the low blood-brain barrier permeability of cyclosporin following a single injection." Again, this is entirely consistent with the present specification, which teaches that "some immunophilin-binding drugs, like cyclosporin A, do not readily penetrate into the brain" but "can be effectively administered by, for example, an intraventricular route of delivery" (page 7).

CONCLUSION

In our judgment, the reasons cited in support of the examiner's rejection do not provide a reasonable basis to question the adequacy of the disclosure provided for the claimed invention. Thus, in our opinion, the PTO has failed to meet the initial burden of

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establishing a prima facie case of unpatentability as to the claims on appeal. Accordingly,
the rejection of the claims under the first paragraph of 35 U.S.C. § 112 is reversed.

REVERSED

Sherman D. Winters
Administrative Patent Judge

Douglas W. Robinson
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

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